

Pediatric Advisory Committee
**Topical Immunosuppressants
Inhibit DNA Repair**

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AGI Dermatics

Freeport, NY

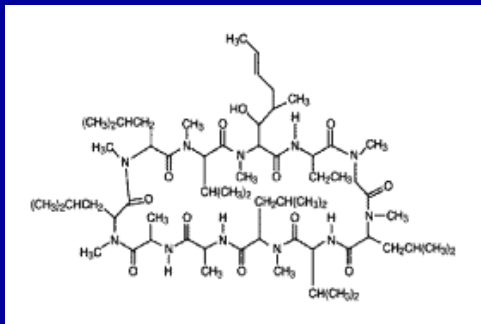
February 15, 2005

Disclaimer

Calcineurin Inhibitors

Immunosuppressants

Cyclosporine A

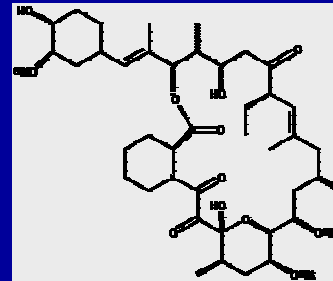


Use: Transplant, iv psoriasis

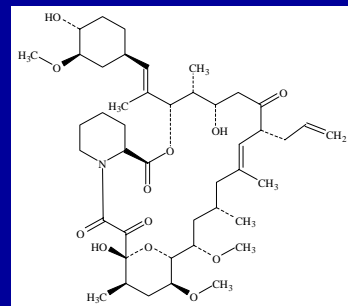
Immunophilin: cyclophilin

Target: **calcineurin**

Ascomycin (FK506) Family



Tacrolimus

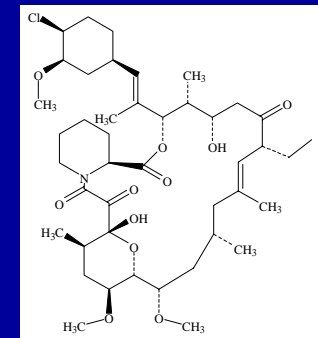


Transplant, Topical AD

FKBP

calcineurin

Pimecrolimus

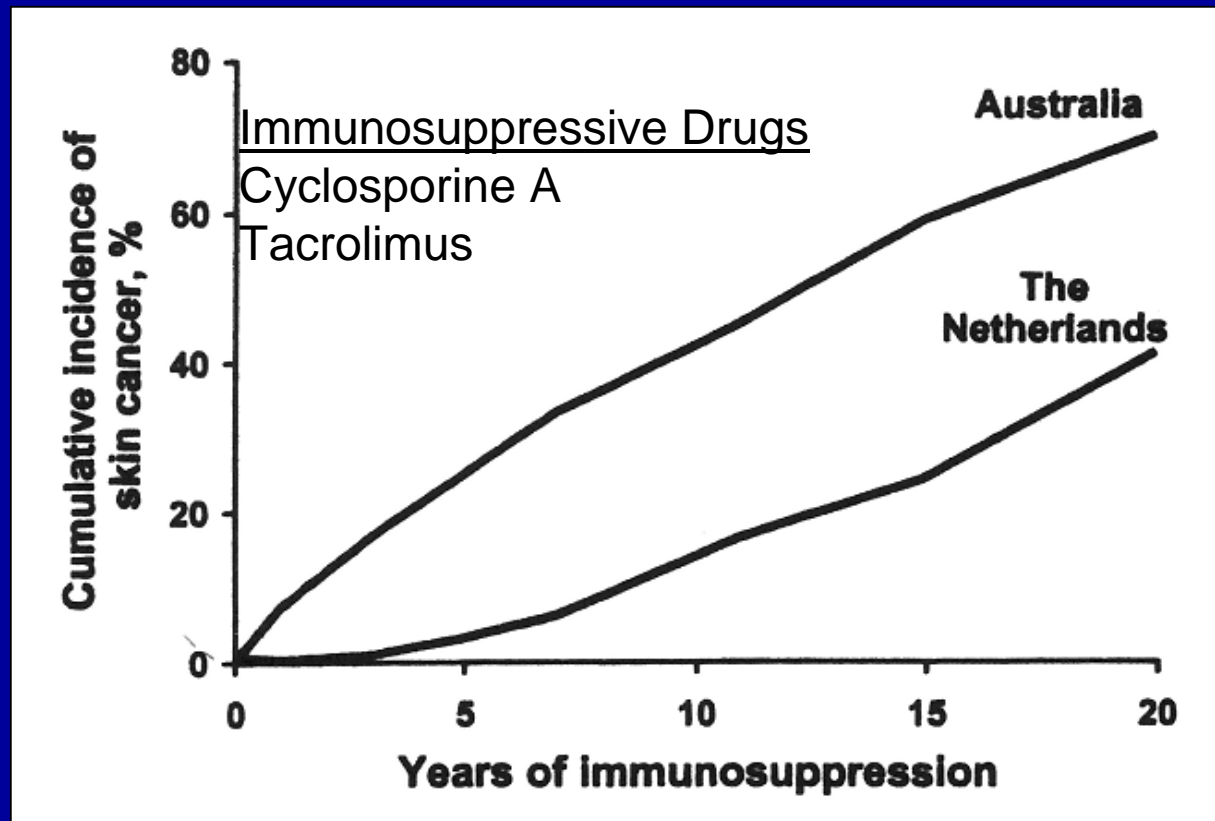


Topical AD

FKBP

calcineurin

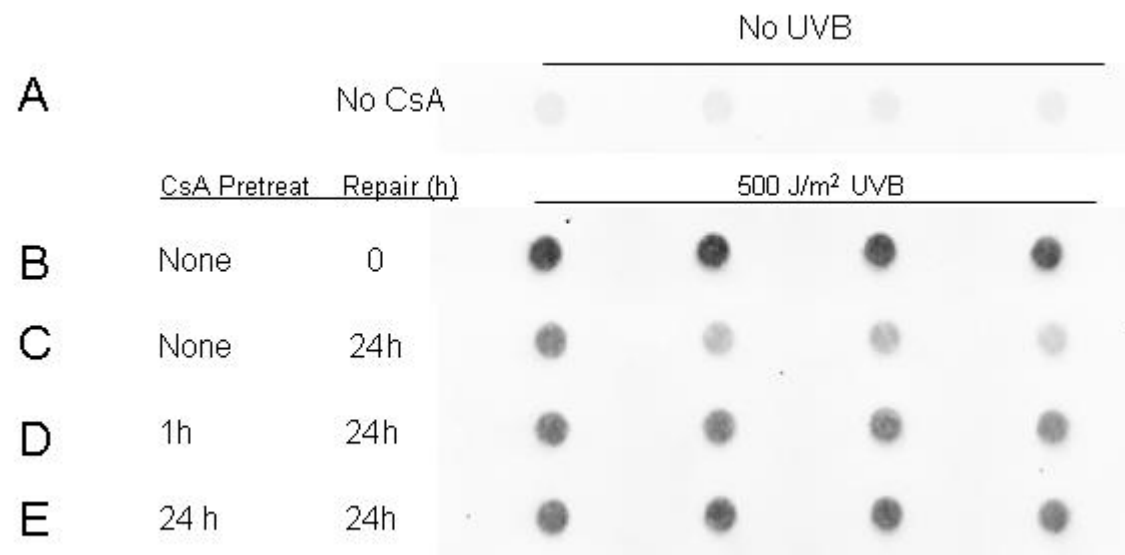
Skin Cancer in Organ Transplant Patients



Berg and Otley, JAAD 47:1-17, 2002

Cyclosporine A Inhibits DNA Repair

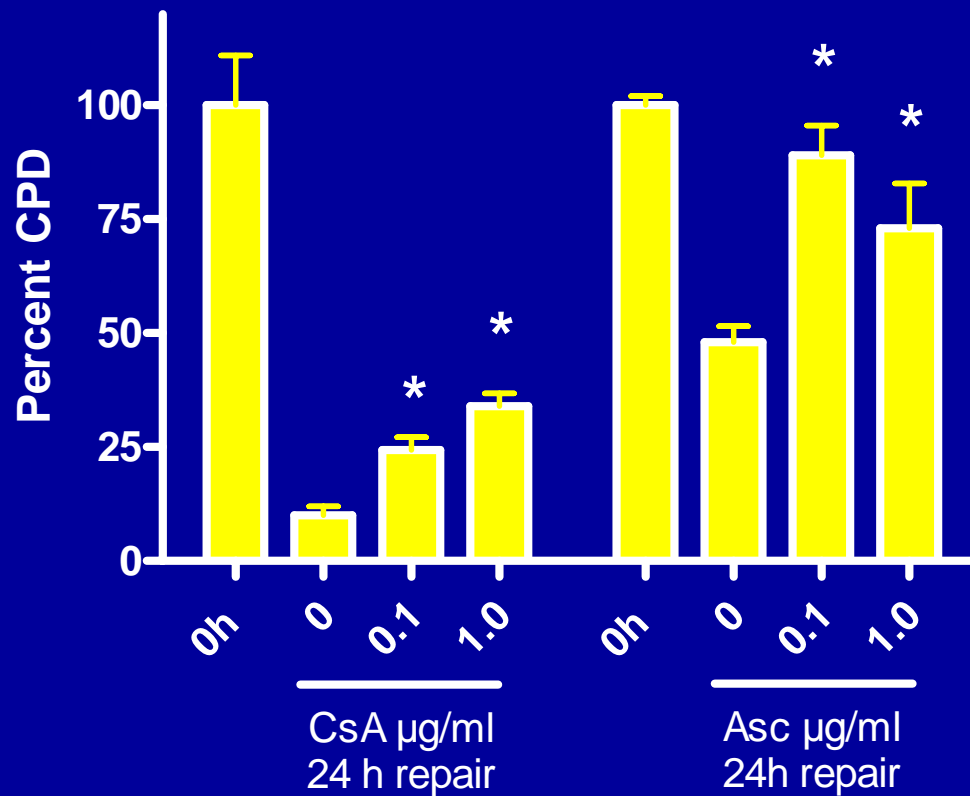
Human Keratinocytes Dot-blots for DNA Damage



Submitted for publication

Calcineurin Inhibitors Reduce DNA Repair

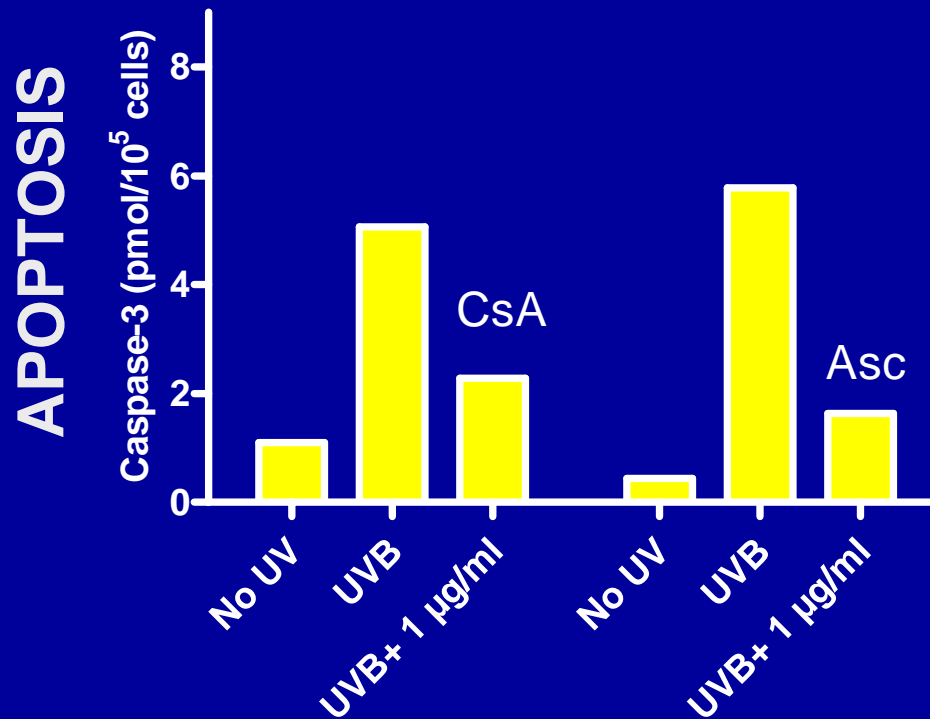
HaCaT Keratinocytes Irradiated with 500 J/m² UVB



Submitted for publication

Calcineurin Inhibitors Reduce Apoptosis

Programmed cell death from excessive DNA damage



Submitted for publication

Skin Cancer

The combination of

- Persistent DNA damage
- Inhibition of apoptosis

are the early steps of skin cancer.

Summarized in: Leffell and Brash, *Scientific American* July 1996, p38

Animal Carcinogenesis Studies

- Cyclosporine A strongly linked to carcinogenesis
Vogt et al., J Invest Dermatol 124:263, 2005
- Topical Tacrolimus accelerated skin carcinogenesis by DMBA
Niwa et al., Br J Derm 149:960, 2003
- Photocarcinogenesis: One study was submitted for each NDA of Tacrolimus and Pimecrolimus. Both studies were significantly flawed because **the vehicle alone accelerated carcinogenesis.**

Human Safety Studies

Published safety studies are
underpowered to detect changes in
skin cancer

≤ 1 year duration is too short

< 100 patients is too few

Longer studies are unpublished

Risk in Childhood UV Exposure

Cumulative UV exposure is a risk factor for non-melanoma skin cancer, esp. SCC

Kricker et al. *Int. J. Cancer* 60:482, 1995

Childhood UV exposure and the number of painful sunburns before age 15 are risk factors for BCC and melanoma

Kricker et al. *Int. J. Cancer* 48:650, 1991

Vlajinac et al. *Acta Oncologica* 39:1, 2000

Jema et al., *JNCI* 92:811, 2000